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The effects of static charge in spacer devices on glucocorticosteroid aerosol deposition in asthmatic patients

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The effects of static charge in spacer devices on glucocorticosteroid aerosol deposition in asthmatic patients. C.J. Kenyon, L. Thorsson, L. Borgström, S.P. Newman. ©ERS Journals Ltd 1998.

ABSTRACT: Electrostatic charge in plastic spacer devices has been shown *in vitro* to reduce delivery of asthma medications intended for inhalation, but the effect of static charge on *in vivo* drug deposition is unknown.

A six-way randomized crossover study was conducted in 10 mild asthmatic patients. Two plastic spacers (Nebuhaler® and Volumatic®) and one metal spacer (Nebuchamber®) were tested. The spacers were used either "primed" or "unprimed". Priming was performed by firing 20 doses of placebo aerosol into a new spacer, hence coating the inner surface with surfactant and minimizing static charge. Unprimed spacers were new and were not treated. Pressurized aerosol canisters delivering budesonide (200 µg Pulmicort®) were radiolabelled with the radionuclide ^{99m}Tc and lung deposition was measured by gamma scintigraphy. The radiolabel was shown to be a valid marker for the drug substance prior to the clinical phase of the study.

Priming significantly increased mean whole lung deposition following inhalation from plastic spacers (Nebuhaler® primed 37.7% and unprimed 26.7%, p=0.01; Volumatic® primed 32.0% and unprimed 22.1%, p=0.02). Priming had no effect on the mean whole lung deposition following inhalation from the Nebuchamber® (primed 33.5% and unprimed 32.9%).

Lung deposition *in vivo* from plastic spacer devices will vary according to the electrostatic charge on the spacer walls. Priming reduces retention of drug on plastic spacer devices and increases lung deposition. Metal spacers are not susceptible to static charge, which should result in more predictable lung deposition.

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Spacer devices are widely used to eliminate problems of poor co-ordination and the "cold Freon" effect in patients using pressurized metered-dose inhalers (pMDIs) [1]. They are often reported to increase drug delivery to the lungs when compared with use of a pMDI alone [2, 3]. The deposition of larger particles in the oropharynx, which results in the unwanted local side-effects of high-dose corticosteroids, can be reduced by using these devices [4]. Large-volume spacer devices are recommended for inhaled steroid doses of 800 µg per day or more, and for administration of inhaled corticosteroids to children <5 yrs of age [5].

The output of drugs from plastic spacers is affected by static charge [6]. Plastic spacers have been shown to retain high static charge on their walls; this attracts airborne drug particles, and the output of drug from such devices is reduced [7–9]. Reducing the static charge by wiping the spacer with an antistatic cloth, or coating the inner walls with an antistatic lining, results in increased drug output *in vitro* [6]. Other pretreatments shown to have a similar effect include washing the spacer with a detergent solution [10] or "priming" the spacer by firing placebo doses so that the inner surfaces are coated with surfactant [11]. An earlier scintigraphic investigation performed at this site [12] showed that very high lung deposition (>30% of the dose) can be achieved from a plastic spacer device that has been primed to reduce static charge, but comparative deposition data using "unprimed" and "primed" spacers in the same individual were not obtained on that occasion.

This investigation has compared the effect of priming on the lung deposition from three spacer devices, two of which were made of plastic and one of metal. This is the first study to compare the effects of priming or not priming spacers in the same population of asthmatic patients, and is only the second study to assess techniques for reducing static charge on spacer devices *in vivo* [13].

Materials and methods

Study design

This was a randomized, six-way crossover study in 10 asthmatic patient-volunteers. Each patient received two doses of 200 µg (total 400 µg) budesonide (Pulmicort®; Astra Draco AB, Lund, Sweden) on each of six occasions. Three spacer devices were tested; two 750 mL plastic spacers (Nebuhaler®; Astra Draco AB, and Volumatic®;

Glaxo Wellcome Ltd, Greenford, UK) and one 250 mL metal spa-cer (Nebuchamber®; Astra Draco AB). Nebuchamber® is a pear-shaped spacer made of steel which provides nonelectrostatic surfaces and, together with the small volume, assures a highly concentrated aerosol [14].

The six study regimens were as follows: 1) pMDI with Nebuhaler®, unprimed; 2) pMDI with Nebuhaler®, primed; 3) pMDI with Volumatic®, unprimed; 4) pMDI with Volumatic®, primed; 5) pMDI with Nebuchamber®, unprimed; and 6) pMDI with Nebuchamber®, primed.

"Unprimed" spacers were new devices used immediately following removal from their packaging materials and remained untreated. Devices were "primed" by firing 20 placebo doses into them in order to coat the inner surfaces with surfactant, approximately 7 days prior to administration of the radiolabelled formulations [11]. Each priming dose was withdrawn from the spacer by a vacuum pump operating at 60 L·min^{-1} for 5 s.

Study population

Ten patient-volunteers (five females and five males; table 1) diagnosed as suffering from mild-to-moderate asthma (forced expiratory volume in one second (FEV_1) 50–104% of predicted values [15], age range 19–66 yrs), were recruited from the Pharmaceutical Profiles Limited asthmatic patient panel. Each patient had demonstrated at least 15% reversibility in either FEV_1 or peak expiratory flow (PEF) in response to an inhaled bronchodilator. The patients were otherwise well. Informed consent was given in writing. Subjects underwent a medical examination in the 21 day period prior to the first dosing and a poststudy medical was performed within 14 days of completion of the last study day. Normal asthma medication was continued throughout the duration of the study. The design and study objectives were approved by the Quorn Research Review Committee, UK, and approval to administer radioactive formulations was given by the Department of Health, UK.

Radiolabelling technique

Budesonide (Pulmicort®) inhalers were radiolabelled by the addition of ^{99m}Tc using a previously described technique [16]. In order to determine the extent to which the distribution of radiolabel across different particle size fractions resembled that of the drug, measurements were performed using a multistage liquid impinger operated at a flow rate of 60 L·min^{-1} [17]. The distribution of "unlabelled" drug in different particle size fractions from inhalers containing no ^{99m}Tc was compared with those of the "labelled" drug and radiolabel from inhalers to which ^{99m}Tc had been added. The stages of the impinger were washed out with ethanol and the washings were assayed for drug content and for radioactivity content by ultraviolet (UV) spectometry and by gamma camera respectively.

Inhalation methods

Prior to inhalation of the radiolabelled dose, patients were trained to inhale at the desired flow until they were adjudged to have mastered the technique. The pMDI canisters were shaken prior to each administration and the pMDIs were fired into the spacer by the operator. Patients were instructed to commence inhaling after approximately 1 s and to take a slow deep inhalation (approximately 15 L·min^{-1}) followed by a 10 s breath-holding pause. Immediately after inhalation, the subjects exhaled through a low-resistance filter (Pall Ultipor, Portsmouth, UK). Administration of the radioactive aerosol was performed with the inhaler connected in series with a Vitalograph metered-dose inhaler (MDI)-Compact Spirometer (Vitalograph, Buckingham, UK). During the inhalation, the inhaled volume, inhaled flow and length of the breath-holding pause were recorded.

Scintigraphic measurements

Immediately after dosing, a posterior and anterior view of the lungs (100 s) and a lateral view of the oropharynx (30 s) were taken using a gamma camera (General Electric Maxicamera, Milwaukee, WI, USA) fitted with a low-energy parallel hole collimator. The gamma camera was coupled to a Bartec Micas V data processing system (Nodecrest Ltd, Byfleet, UK). Images of the actuator, plastic spacers and exhalation filter were also recorded. The steel

Table 1. – Demographic details of patients studied, including lung function measurements before and after an inhaled bronchodilator, and asthma medication at the time of the study

Subject No.	Sex	Age yrs	Reversibility: Pre-bronchodilator FEV_1 L*	Reversibility: Post-bronchodilator FEV_1 L*	Reversibility: % Reversibility	Asthma medication
1	F	66	259*	307*	18.5	ISB, IC
2	F	58	2.17	2.53	16.6	ISB, IC
3	M	56	2.17	2.50	15.2	ILB, IC
4	F	65	1.30	1.74	33.8	ISB, IC, IA, OM
5	M	42	2.85	3.35	17.5	ISB, IC
6	M	19	576*	721*	25.2	ISB
7	M	63	1.37	1.59	16.1	ISB, IC, OM
8	F	55	1.96	2.31	17.8	ISB, IC
9	M	53	2.11	2.44	15.6	ISB, IC
10	F	23	308*	357*	15.9	ISB, IC

*: Data for subjects Nos. 1, 6 and 10 are peak expiratory flows (L·min^{-1}). ISB: inhaled short-acting beta-agonist; IC: inhaled corticosteroid; ILB: inhaled long-acting beta-agonist; IA: inhaled anti-cholinergic; OM: oral methylxanthine; M: male; F: female; FEV_1: forced expiratory volume in one second.

composition of Nebuchamber® would have resulted in gamma ray attenuation, and for this device the plastic mouthpiece was removed and imaged separately after use; the metal spacers themselves were washed carefully with 100 mL of methanol and the washings subsequently imaged to determine spacer retention values.

The geometric means of the anterior and posterior counts were calculated and corrections were made for tissue attenuation of gamma rays [18]. Oropharyngeal deposition was taken as the sum of radioactivity recorded over mouth, pharynx, oesophagus and stomach. From these measurements the metered dose could be fractionated into that: 1) in the lungs; 2) in the oropharynx; 3) in the actuator; 4) in the spacer; and 5) in the exhaled air.

On one of the study days, a posterior lung ventilation scan was performed using the radioactive inert gas ^{81m}Kr. This determined the whereabouts of the lung edges and was used to divide the lung images following budesonide inhalations into central, intermediate and peripheral zones and hence to determine the amount of aerosol deposited in each zone. The regions were defined as previously described [19, 20] and the peripheral zone/central zone deposition ratio was calculated.

Clinical measurements

On each study day, FEV_1 and PEF were recorded predose and then at least 30 min post-dosing. Subjects were only dosed if the pre-dose FEV_1 was within 15% of its value at the pre-study screening. The best of three technically acceptable attempts was taken as the true measure of lung function at each time point.

Table 2. – Percentage distribution of drug and radiolabel delivered from pressurised metered-dose inhalers within a multistage liquid impinger system

		Distribution %		
	Diameter of particles collected μm	Unlabelled drug (n=5)	Labelled drug (n=4)	Radiolabel (n=4)
Actuator		4.3 (0.5)	3.7 (0.3)	4.7 (2.4)
Throat		61.1 (2.2)	65.1 (1.1)	65.1 (2.9)
Stage 1		1.0 (0.1)	1.2 (0.3)	1.3 (0.5)
Stage 2	6.8–13.0	3.5 (0.4)	2.8 (0.5)	2.4 (1.1)
Stage 3	3.1–6.8	12.5 (1.7)	11.8 (0.6)	8.3 (0.9)
Stage 4	<3.1 μm	17.6 (2.2)	15.6 (1.0)	18.3 (2.2)
FPF		30.1 (1.8)	27.4 (0.7)	26.6 (2.3)

Values are mean (SD) or range. Fine particle fraction (FPF) = Stage 3 + Stage 4.

Statistical analysis

The Wilcoxon rank sum test for paired data was used to examine the deposition figures for primed and unprimed spacers. A p-value of less than or equal to 0.05 was taken to indicate statistical significance.

Results

Radiolabelling measurements

The *in vitro* multistage liquid impinger measurements showed that the particle size distributions of: 1) drug from canisters which had not been radiolabelled (unlabelled drug); 2) drug from canisters which had been radiolabelled (labelled drug); and 3) radiolabel, were similar (table 2). The mean fine particle fraction (FPF) (particles <6.8 μm diameter) penetrating beyond stage 2 of the impinger for unlabelled drug was 30.1%, compared with 27.4% for labelled drug and 26.6% for the radiolabel. The ratio of the radiolabel FPF to that of the unlabelled drug was 0.88. It was concluded that the radiolabelling procedure had not changed the particle size distribution of the budesonide, and that the radiotracer was an accurate marker for the presence of the drug.

Deposition data

As shown in table 3, priming resulted in a significant decrease in the mean percentage of the dose retained in the plastic spacers (Nebuhaler® primed 32.3% and unprimed 56.0%, p<0.01; Volumatic® primed 46.8% and unprimed 62.3%, p<0.01). In contrast, mean spacer retention values for the metal Nebuchamber® were similar irrespective of priming (primed 27.5% and unprimed 29.0%).

Priming large volume plastic spacers resulted in a significant increase in mean lung deposition (table 3) when compared with unprimed devices (Nebuhaler® primed 37.7% and unprimed 26.7%, p=0.01; Volumatic® primed 32.0% and unprimed 22.1%, p=0.02). However, mean lung depositions for primed (33.5%) and unprimed (32.9%) Nebuchamber® spacers were not significantly different. For both the plastic spacers the increase in whole lung deposition observed following priming was a result of an increase in deposition in each of the three lung regions, *i.e.* there was no change in the peripheral zone/central zone deposition ratio following priming (table 3).

Table 3. – Percentage deposition for the three spacer devices

	Nebuhaler®			Volumatic®			Nebuchamber®		
Region	Unprimed	Primed	p-value	Unprimed	Primed	p-value	Unprimed	Primed	p-value
Whole lung %	26.7 (6.2)	37.7 (12.0)	0.01	22.1 (10.1)	32.0 (10.8)	0.02	32.9 (10.1)	33.5 (12.7)	NS
Central lung %	8.1 (2.2)	11.7 (3.8)	<0.05	6.6 (3.5)	9.3 (3.1)	<0.05	9.3 (3.2)	9.6 (3.7)	NS
Intermediate lung %	9.6 (2.3)	13.6 (4.6)	<0.05	8.1 (3.8)	11.8 (4.0)	<0.05	12.2 (4.4)	12.4 (5.2)	NS
Peripheral lung %	9.1 (2.7)	12.5 (4.5)	<0.05	7.5 (3.1)	11.0 (4.2)	<0.05	11.4 (3.6)	11.5 (4.4)	NS
Peripheral/Central ratio	1.2 (0.4)	1.1 (1.3)	NS	1.2 (0.3)	1.2 (0.3)	NS	1.3 (0.4)	1.2 (0.3)	NS
Oropharyngeal %	11.4 (6.7)	23.7 (12.3)	<0.01	7.6 (4.2)	12.8 (7.1)	<0.01	26.5 (12.8)	27.2 (12.6)	NS
Spacer retention %	56.0 (5.1)	32.3 (9.5)	<0.01	62.3 (10.9)	46.8 (9.2)	<0.01	29.0 (4.8)	27.5 (6.0)	NS
Actuator %	5.1 (1.0)	5.7 (2.1)	NS	7.2 (1.8)	7.3 (1.8)	NS	11.0 (1.7)	11.1 (2.4)	NS
Exhalation filter %	0.8 (0.3)	0.7 (0.4)	NS	0.9 (0.4)	1.1 (0.5)	NS	0.6 (0.3)	0.6 (0.3)	NS

Values are mean (SD). A p-value is are given for comparison between primed and unprimed spacers. NS: nonsignificant.

Table 4. – Inhaled flow, inhaled volume and breath-holding pause for the six regimens

	Nebuhaler®		Volumatic®		Nebuchamber®	
	Unprimed	Primed	Unprimed	Primed	Unprimed	Primed
Inhaled flow L·min^{-1}	16.9 (6.2)	14.9 (3.1)	13.6 (3.5)	15.1 (4.4)	14.0 (2.9)	15.2 (4.2)
Inhaled volume L	1.81 (0.62)	2.05 (0.63)	1.53 (0.71)	1.69 (0.52)	2.82 (0.94)	2.71 (1.05)
Breath-holding pause s	11.5 (2.2)	10.3 (1.3)	10.4 (1.1)	10.2 (1.7)	9.4 (1.5)	10.2 (2.2)

Values are mean (SD).

Table 5. – Forced expiratory volume in one second (FEV_1), before and 30 min after inhalation of budesonide

	FEV_1	
	Pre-inhalation	Post-inhalation
Nebuhaler®		
Unprimed	2.78 (1.00)	2.80 (0.98)
Primed	2.68 (0.94)	2.68 (0.94)
Volumatic®		
Unprimed	2.73 (0.97)	2.74 (0.99)
Primed	2.69 (0.96)	2.72 (0.97)
Nebuchamber®		
Unprimed	2.73 (0.97)	2.74 (0.99)
Primed	2.69 (0.96)	2.72 (0.97)

Values are mean (SD).

Mean oropharyngeal deposition was low for each of the three spacer devices although results for the Nebuchamber® were higher when compared with the two plastic spacers (unprimed 11.4, 7.6 and 26.5%; primed 23.7, 12.8 and 27.2%, for the Nebuhaler®, Volumatic® and Nebuchamber® spacers, respectively). Oropharyngeal deposition was significantly ($p<0.01$) increased by priming the two plastic spacers, but not by priming the Nebuchamber®.

Inhalation details

The mean parameters of inhalation are given in table 4. The technical performance of the inhalations was good with the inhalation parameters close to targeted values. Inhaled volumes averaged higher for the Nebuchamber® than for the two plastic spacers, but there were no differences between the treatment regimens in either inhaled flow or breath-holding pause.

Lung function

Within each subject, pre-dose FEV_1 values were similar on each study day (table 5), and there were no significant changes in lung function following inhalation of budesonide.

Discussion

The surface of a plastic spacer device may acquire a high electrostatic charge, and this may affect the delivery of drug particles to the lungs. There have been several reports in the literature of *in vitro* studies in which the output from plastic spacer devices has been shown to increase following pretreatment of the spacer walls, carried out in order to reduce static charge [6–8]. This is not surprising, since the higher the static charge on the walls of the spacer becomes, the more likely it is that drug will be deposited there and be unavailable for inhalation. DEWSBURY *et al*. [10] correlated the static voltage on a plastic spacer device handled by several different techniques with the FPF of salbutamol from the spacer, and an inverse relationship between static voltage and fine particle fraction was confirmed. These *in vitro* findings have been followed by a single clinical investigation to date. CLARK and LIPWORTH [13] examined the effect of prewashing spacers on lung bioavailability of salbutamol following inhalation from Volumatic®. In this case, prewashed spacers were shown to be as effective as an antistatic lining in reducing the effects of static charge on salbutamol delivery *in vivo*.

The present investigation is the first scintigraphic study in which the effect of priming plastic spacer devices on lung deposition has been assessed in a group of asthmatic patients, and it was clearly demonstrated that priming plastic spacers resulted in an increase in lung deposition. Optimal inhalation manoeuvres (inhaled flow ~15 L·min^{-1}) were achieved when administering the radiolabelled aerosol *via* both primed and unprimed spacers, and the very high lung deposition values observed following priming can be attributed partly to the priming procedure itself and partly to inhalation technique. Although inhaled volumes were higher for the Nebuchamber® than for the two plastic spacers, it is unlikely that this influenced lung deposition, since the volumes were sufficient to empty the spacer contents for all three devices. Whilst clinical trials can examine the efficacy and safety of drugs delivered by spacers, it is impossible to obtain values for spacer retention from these studies alone. In addition to assessing lung deposition, gamma scintigraphic studies [21] can quantify spacer retention, which in this study has enabled the mechanisms responsible for the increase in lung deposition to be clearly elucidated.

The process of priming coats the inner surface of the spacer with a layer of surfactant. In a plastic spacer, this acts as a conducting layer, and reduces the static charge thereby reducing aerosol deposition on the spacer walls [22]. By contrast, metal spacers do not carry a static charge, and hence the process of priming does not result in any reduction in retention on the spacer walls or improvement in lung deposition. Irrespective of its state of priming, Nebuchamber® spacer gave lung deposition values equivalent to those from the primed plastic spacers, despite having a volume only one third that of Nebuhaler® and Volumatic®. BISGAARD *et al.* [23] compared the passive disappearance half time of aerosol ($t_{1/2}$) in primed and unprimed Nebuhaler® and Nebuchamber®. Priming increased the $t_{1/2}$ in Nebuhaler® from 9 to 32 s, while a normal cleaning procedure reduced the $t_{1/2}$ to its original value. By contrast, the $t_{1/2}$ in the Nebuchamber® was 27 s, and this was independent of priming or washing procedures.

Whilst priming of plastic spacer devices may reduce drug retention and increase lung deposition, washing the spacer may remove the surfactant layer, resulting in the

spacer resuming to its original highly charged state. The spacer could then go through cycles of high and low drug delivery, as the surfactant builds up on the walls with use, and is then removed during washing. Delivered drug may be low immediately following washing and gradually increase with use until the time that the spacer is next washed. This situation will lead to intersubject variation in dosage as well as intrasubject variation, since patients will approach cleaning their spacers in different ways. Metal spacers overcome this problem, offering the possibility of more predictable drug delivery, which may in turn result in greater ease in the control of a patient's asthma.

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